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Catarina Metelo Coimbra dos Santos Ferreira

Placenta Artificial: Avanços Recentes e Potenciais Aplicações Clínicas

Artificial Placenta: Recent Advances and Potential Clinical Applications

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NOME

CATARINA METELO COIMBRA DOS SANTOS FERREIRA

NÚMERO DE ESTUDANTE	E-MAIL
201200152	catarinametelocoimbra@hotmail.com

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ORIENTADOR

PROFESSOR DOUTOR ROBERTO RONCON-ALBUQUERQUE

COORIENTADOR (se aplicável)

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Assinatura conforme cartão de identificação: Catarina Metelo Coimbra dos Santos Ferreira

ARTIFICIAL PLACENTA: RECENT ADVANCES AND POTENTIAL CLINICAL APPLICATIONS

Catarina Metelo-Coimbra and Roberto Roncon-Albuquerque Jr[1,2]

1. Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine of Porto, PORTUGAL
2. Department of Emergency and Intensive Care Medicine, Hospital de S. João, Porto, PORTUGAL

Abbreviated Title: Recent Advances in the Artificial Placenta.

Correspondence address:

Roberto Roncon-Albuquerque Jr, MD PhD

Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine of Porto and Department of Emergency and Intensive Care Medicine Hospital de S. João

Al. Prof. Hernâni Monteiro, Porto 4200-319, PORTUGAL

Tel.: +351 916 454 074

Fax: +351 225 025 766

E-mail: rra_jr@yahoo.com

ABSTRACT

Lung immaturity remains a major cause of morbidity and mortality in extremely premature infants. Positive-pressure mechanical ventilation, the method of choice for respiratory support in premature infants, frequently promotes by itself lung injury and a negative impact in the circulatory function. Extracorporeal lung support has been proposed for more than 50 years as a potential alternative to mechanical ventilation in the treatment of severe respiratory failure of extremely premature infants. Recent advances in this field included the development of miniaturized centrifugal pumps and polymethylpentene oxygenators, as well as the successful use of pump-assisted veno-venous extracorporeal gas exchange systems in experimental artificial placenta models. This review, which includes studies published from 1958 to 2015, presents an update on the artificial placenta concept and its potential clinical applications. Special focus will be devoted to the milestones achieved so far and to the limitations that must be overcome before its clinical application. Notwithstanding, the artificial placenta stands as a promising alternative to mechanical ventilation in extremely premature infants.

Keywords: Artificial placenta; bronchopulmonary dysplasia; extracorporeal membrane oxygenation; extremely premature infant; respiratory distress syndrome.

INTRODUCTION

According to the World Health Organization, 15 million premature infants are born every year, with almost 1 million deaths directly attributed to prematurity[1]. Although all premature infants are at risk for complications, extremely premature (EPT) infants, born at or before 28 weeks of gestation, suffer the greatest morbidity and mortality[1]. Respiratory distress syndrome and bronchopulmonary dysplasia remain a major cause of morbidity and mortality in EPT infants[2]. This relates with pulmonary immaturity, given that EPT infants are born during the canalicular period of lung development, characterized by capillarization and pulmonary acini morphogenesis, with insufficient surfactant production[3].

Positive-pressure mechanical ventilation with high oxygen concentrations remains the method of choice to provide lung support in preterm infants with severe respiratory failure[4]. However, mechanical ventilation in preterm infants promotes, by itself, lung injury that negatively impacts survival. The known direct mechanisms of ventilator-induced lung injury are barotrauma, volutrauma and atelectrauma[5]. These mechanisms promote biotrauma with capillary endothelium, alveolar epithelium, and basal membrane damage, which results in fluid, protein and blood extravasation into the airways, alveoli, and pulmonary interstitium, with consequent surfactant inhibition and activation of local and systemic inflammatory responses[6]. Mechanical ventilation also adversely affects the circulatory function of preterm infants, reducing pulmonary blood flow and left ventricular output[7,8]. In fact, positive-pressure mechanical ventilation decreases the alveolar/capillary transmural pressure gradient, causing compression of the intra-alveolar capillaries, which increases pulmonary vascular resistance, therefore decreasing pulmonary blood flow[9]. Further increases in airway pressure and pulmonary vascular resistance may sustain pulmonary arterial pressures above systemic arterial pressures, potentiating continued right-to-left shunt through the ductus arteriosus. The effect of positive-pressure ventilation is not limited to the pulmonary vasculature, with direct compressive effects observed on the newborn heart, resulting in reduced cardiac performance and ventricular output[10]. This could be particularly relevant in the immature myocardium of the preterm heart that presents low contractility with an inability to cope with increasing afterload in the days after birth[11].

In light of these limitations, extracorporeal lung support has been proposed more than 50 years ago as a potential alternative to mechanical ventilation in the treatment of severe respiratory failure of EPT infants[12]. Its main benefits reside in the fact that, by bypassing the lungs completely, the AP avoids potential barotrauma resulting from mechanical ventilation. However, by then, artificial organ technology was still in its infancy and the understanding of EPT pathophysiology was very limited. More recently, important developments in extracorporeal lung assist technology were observed, fostering a renewed interest in artificial placenta (AP) research.

In this review, an update on the AP concept and its potential applications is presented. Special focus will be devoted to the milestones achieved so far and to the major limitations that must be overcome before its clinical application.

METHODS

Eligible studies were identified by an electronic search of PubMed and Scopus, involving studies published from 1958 to 2015. The sensitive search strategy combined the following keywords: *artificial placenta*; *bronchopulmonary dysplasia*; *extracorporeal lung assist*; *extracorporeal membrane oxygenation; extremely premature infants*; *polymethylpentene oxygenator*; and *respiratory distress syndrome*. All articles and cross-referenced studies from retrieved articles were screened for pertinent information and reviewed by both Authors.

Inclusion criteria consisted in experimental and systematic review articles, published as original studies, with available abstract. Publications not written in English or not related to the neonatal period were excluded.

ARTIFICIAL PLACENTA: THE CONCEPT

The terminology describing extracorporeal life support (ECLS) in premature infants is divided in three categories, established according to the gestational age[13]: *i*) neonatal ECMO: for infants of at least 34 weeks of gestation (moderate to late preterm newborns[1]); this technique is successfully used in clinical practice for more than 30 years; *ii*) preemie ECMO: for premature infants between 29 and 33 weeks of gestation (very preterm newborns); although technically feasible, reduced survival and increased rates of intra-ventricular hemorrhage have been reported[14]; and *iii*) artificial placenta: for EPT infants, born before 28 weeks; the AP currently remains under experimental research.

Therefore, the AP concept consists in extracorporeal membrane gas exchange (blood oxygenation and extracorporeal CO_2 removal) for EPT infants with immature pulmonary system and severe respiratory failure, as a bridge to the development of native lung function[8]. The AP does not include provision of other placental functions such as nutrient or metabolic product exchange.

AP models are generally defined by the following characteristics [8,13,15,16]: *i*) extracorporeal lung support with preservation of fetal circulation: either the umbilical artery (pumpless arterio-venous ECLS, AV-ECLS) or a central vein (pump-assisted veno-venous ECLS, VV-ECLS) are used for blood outflow from the patient to the extracorporeal circuit; the umbilical vein is always used for inflow to the patient from the extracorporeal circuit[17] (Fig. 1); *ii*) low partial pressure of oxygen, given that oxygen-binding capacity of fetal hemoglobin and hematocrit are increased; *iii*) absence of positive-pressure mechanical ventilation; *iv*) simulated fetal breathing with fluid-filled lungs; *v*) biocompatibility of the extracorporeal circuit inner surfaces in direct contact with blood; high levels of systemic anticoagulation associated with an unacceptable risk of intracranial hemorrhage in EPT infants[18].

Pump-assisted VV-ECLS systems presents several advantages when compared to pumpless AV-ECLS[17]: *i*) arterial vessel cannulation is not required; cannulation of umbilical arteries in EPT infants is technically challenging and frequently complicates with vessel spasm; *ii*) an external blood reservoir is not required given that the EPT infant's own venous system is used as blood reservoir; *iii*) it operates in parallel with systemic circulation, therefore not increasing afterload of the fetal heart; differently, pumpless AV-ECLS operates in series with systemic circulation, increasing the fetal heart workload that can complicate with high-output heart failure.

Membrane lung permeability to O_2 and CO_2 is a critical factor influencing AP performance. Silicone rubber membranes were initially used, composed of a permeable non-porous polymeric material with loosely packed polymeric chains[19]. Another type of oxygenator is the hollow-fiber membrane, which has woven capillary tubes composed of microporous polypropylene[20]. Despite higher gas permeability, polypropylene membranes are less frequently used given the high plasma leakage risk with increased extracorporeal circuit blood pressures[20]. Moreover, silicone rubber membranes present higher biocompatibility when compared with polypropylene fibers for long-term ECLS[21].

Polymethylpentene (PMP) oxygenators have been used in clinical practice for a decade[22]. PMP fibers have an asymmetric pore structure with a very thin dense outer skin that allows gas transference while suppressing the direct contact of blood and gas across micropores[23]. These features enhance durability and greatly reduce plasma leakage[23]. Moreover, PMP oxygenators present more efficient priming, reduced hemodynamic resistance and better preservation of coagulation proteins[21].

EARLY MILESTONES

Following the development and implementation of the heart-lung machine, it was soon recognized that this concept could be similarly applied to the treatment of severe respiratory failure of the premature infant[24]. In 1958, Westin et al. prolonged the life of previable human fetuses by cannulating the umbilical vessels and circulating the fetal blood through a rotating oxygenator[25]. When injecting regular doses of glucose solution, the fetal heart continued to beat for a period up to 12 hours[25]. The fetuses were maintained in a warm artificial amniotic fluid bath[25].

Callaghan et al. were the first to develop the AP concept in animal experiments, back in 1961. A pump-assisted VV-ECLS circuit with a rotating disc oxygenator was used in eight sheep[26]. Blood outflow from the animal to the extracorporeal circuit was performed via both femoral and jugular veins, while inflow to the animal from the extracorporeal circuit was made either through the right atrium or the right ventricle[26]. In 1962, a period of up to 2.5 hours survival of mongrel dogs using this procedure was reported[27].

These achievements have been overcome by Lawn and McCance[28], who conceived a pumpless AV-ECLS circuit with a dialyzer that was tested in previable pig fetuses. Blood drained from the umbilical arteries circulated through the oxygenator and then through cellophane tubing immersed in a suitable rinse. Blood returned to the umbilical vein without requiring external pump assistance[28]. A similar perfusion apparatus was constructed in 1964 by Alexander et al., but the dialyzer was excluded[29]. It was concluded from their experiments that a perfusion system with constant volume would be necessary, due to changes in venous pressure[29].

Meanwhile, SenGupta et al. described a portable, self-contained and self-powered AP consisting of a flexible, inert silicone elastomer membrane oxygenator and a pump[30]. Their first experiment had eleven out of sixteen survivors during up to 5 hours of connection to the AP[30]. Two years later, there were sixteen survivors out of twenty dogs, and most perfusions took more than 2 hours. Though satisfactory oxygenation was obtained, the short period of survival was considered unsafe[31].

Significant progress was achieved in 1969 by Zapol et al.[32], when a premature lamb fetus was totally sustained by extracorporeal perfusion using a silicone-membrane blood oxygenator[32]. The animal received parenteral nutritional support and remained metabolically stable for up to 55 hours. A study with ten lamb fetuses using angiocardiographic techniques was presented the following year[33]. Zapol et al. also described the modulation of ductus arteriosus and pulmonary blood flow by blood oxygen tension in their AP model[34].

Efforts on the development of an AP were almost entirely abandoned by 1979, when a completely different approach to treat severe respiratory failure in premature infants was implemented: positive-pressure mechanical ventilation[35,36]. This led to a dramatic improvement of premature infants' survival, although many problems remained[37]. Compared with positive-pressure mechanical ventilation, the AP was at that time too complex and unsafe for clinical use leading to a gap of research in the next decade.

In 1987, Kuwabara et al.[38] developed a novel AP system. They compared two types of circuits, with and without a blood reservoir, using goat fetuses. In the first group, the duration of incubation was increased to 165 hours, in contrast to the 8 hours achieved by the control group[38]. The oxygenator was made of silicone, and blood was drained from the umbilical arteries and returned to the umbilical vein[38]. This was the first report on animal experiments of successful long-term (up to 7 days) AP support. Several improvements were made to this novel AP system, including alterations in fetal catheterization and addition of a dialyzing system to the extracorporeal circuit, which allowed the survival of goat fetuses up to 236 hours[39].

In 1993, continuing this work, Unno et al. tried a new protocol to study the influence of body movement on goat fetuses' survival[40]. It was demonstrated that AV-ECLS with umbilical blood access could support premature goat fetuses for up to 3 weeks[40]. The following studies focused on fetal hemodynamics, such as goat fetal ductal blood velocity through Doppler echocardiography[41] and the effect of prostaglandin E1[42]. This last experiment suggested that the administration of prostaglandin E1 prevented the constriction of ductus arteriosus, a phenomenon that was found to disturb fetal circulation to the AP[43]. This research group also compared four different methods to control blood flow in an AV-ECLS circuit, concluding that the control of extracorporeal circulation flow by altering the circuit resistance was one of the main contributing factors to the success of long-term incubation[44].

In 1998, Sakata et al. reported the successful use of a centrifugal pump, which allowed higher extracorporeal flow rates[45]. This group used polyolefin hollow fiber membrane oxygenators, which contributed to low circuit resistance[45]. In the same year, Yasufuku et al. refined the AP concept by performing upper tracheal ligation, which maintained lung expansion and protected from meconium aspiration[46,47].

RECENT MILESTONES

In 2012 Gray et al.[48], from the University of Michigan ECLS Laboratory, hypothesized that a pump-assisted VV-ECLS circuit would preserve systemic fetal circulation while providing adequate extracorporeal gas exchange[48]. The right jugular vein was cannulated for outflow from the animal to the extracorporeal circuit, whereas an umbilical vein was used for blood inflow to the animal from the extracorporeal circuit[48]. Blood cavitation was reduced, since blood was passively drained from the right atrium[48]. A miniaturized polypropylene hollow fiber oxygenator was used. The experiment was successful, being the first report of a 24-hour survival of five lamb fetuses using a pump-assisted VV-ECLS circuit. Continuing this work, seven lambs were incubated on a dry heated waterbed and maintained on VV-ECLS for up to 70 hours[49]. This AP model was able to provide hemodynamic stability and efficient extracorporeal gas exchange, with preservation of cerebral perfusion for an extended period of time[49]. No signs of gross or microscopic intra-ventricular hemorrhage were found despite systemic anticoagulation with heparin[49].

In 2015, Bryner et al. compared a pump-assisted VV-ECLS system with positive-pressure mechanical ventilation in EPT lamb fetuses[16]. Four lambs were successfully supported for 1 week using a polypropylene oxygenator and a rotary pump[16]. Differently, lambs treated with positive-pressure mechanical ventilation survived on average less than 4 hours, despite the use of exogenous surfactant and steroids[16]. No evidence of intracranial hemorrhage was observed. The main issues faced by researchers were directly related to cannulation, with one case of pericardial tamponade and arrhythmias[16].

Besides the improvements in extracorporeal circuit configuration, important advances were achieved in oxygenator technology. Arens et al.[50] developed a miniaturized oxygenator to be used in AP models. This research group catheterized lambs through two umbilical arteries and two umbilical veins, and the fetuses were kept in a warming bed. Their oxygenator, NeonatOx, was placed as close as possible to the lambs, allowing short tubing and low circuit resistance[50]. Furthermore, the oxygenator was miniaturized to a priming volume of only 20 ml. This reduced device surface area, decreasing thrombogenesis and inflammation[50]. NeonatOx allowed successful extracorporeal gas exchange for 6 hours in six out of seven animals[51]. One limitation related to the durability of umbilical vascular accesses, since artificial amniotic medium submersion was not performed [51].

Meanwhile, Canadian investigators designed a microfluidic oxygenator with efficient gas exchange[20]. Four different gas permeable membranes were tested using human blood. The porous polydimethylsiloxane membrane had the highest gas exchange rate[20]. Recently, further improvements were performed to this oxygenator[52], with the novel device being modifiable according to the EPT infants' body weight. This microfluidic oxygenator was tested in piglets during 4 hours[52].

FUTURE DIRECTIONS

Although much progress has been made in the AP field and despite the different models studied so far (Table 1 and Table 2), several limitations still preclude its clinical application.

Regarding the extracorporeal circuit itself, pump-assisted VV-ECLS models have shown many advantages over pumpless AV-ECLS circuits. Although its simplicity is appealing, the use of pumpless AV-ECLS in EPT infants seems technically impracticable due to the small size and tortuosity of the umbilical arteries, as well as to the need of prolonged extracorporeal lung support and hemodynamic stability.

Concerning anticoagulation, the development of novel biomaterials will presumably improve surface biocompatibility of the extracorporeal circuit, reducing (or even eliminating) the need for systemic anticoagulation, importantly decreasing intracranial hemorrhage risk[18]. In this regard, research is underway towards the development of non-thrombogenic surface extracorporeal circuit coating[53,54].

Artificial placenta miniaturization will also be improved, decreasing extracorporeal surface area and circuit resistance[51]. The use of PMP oxygenators, which present high durability and reduced plasma leakage, is a predictable next step, given its successful use in adult ECMO [23].

Further studies are required to show that the lung is protected and continues to mature during AP support. This implies that lung development between the stages of birth, AP support and progression to air breathing needs to be demonstrated and documented.

Concerning the brain, studies need to show that there is adequate brain perfusion and that this organ is protected without bleeding or white matter injury during AP support. This is essential given that, regarding neurological complications, the majority of sequelae appear to be related to hypoxemia and hemodynamic instability that occurs before the onset of ECLS[55].

The impact of the AP in the cardiovascular, gastrointestinal and renal systems also deserves further investigation. Cardiovascular stability during pump-assisted VV-ECLS in EPT infants also needs to be confirmed, before establishing this configuration as the preferred AP circuit.

The ability of EPT infants to wean from AP support without major lung sequelae is a central issue that needs further demonstration. This will impact on clinical criteria for AP use, which remain to be established.

CONCLUSION

Lung immaturity still associates with high morbidity and mortality in EPT infants. Extracorporeal lung support has been proposed for more than 50 years as a potential treatment of severe respiratory failure of EPT infants. Recent progresses in extracorporeal circuit biotechnology renewed the interest in experimental and clinical AP research. Notwithstanding the several challenges remaining, the AP remains an attractive potential alternative for EPT infants failing positive-pressure mechanical ventilation. The successful application of the AP into clinical practice would definitely be a milestone in neonatal medicine.

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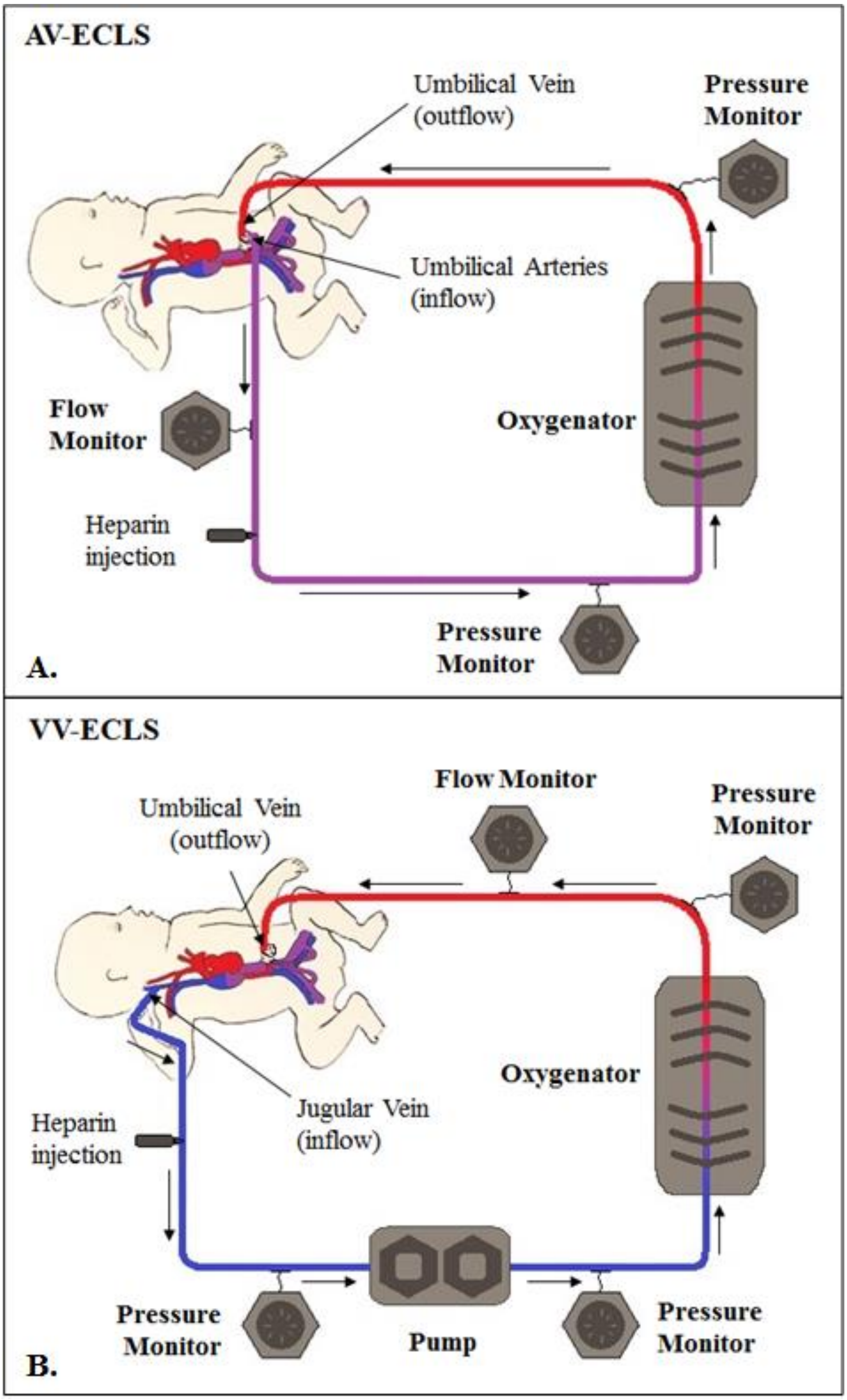
FIGURE 1


AV-ECLS
Umbilical Vein
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Oxygenator
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VV-ECLS
Flow Monitor
Umbilical Vein
(outflow)
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Monitor
Oxygenator
Jugular Vein
(inflow)
Heparin
injection
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FIGURE LEGEND

Figure 1. Artificial placenta circuit configurations. (A) Pumpless arterio-venous extracorporeal lung support (AV-ECLS): blood inflow to the extracorporeal circuit is performed by cannulation of umbilical arteries; the oxygenated blood is then returned to EPT infant through the umbilical vein. (B) Pump-assisted veno-venous extracorporeal lung support (VV-ECLS): blood is drained from central vein(s) (e.g. internal jugular vein); the oxygenated blood is then returned to EPT infant through the umbilical vein.

TABLE 1 - Overview of early experiments performed with several AP models

Reference	Year	Model	Circuit	Oxygenator	Pump	Submersion	Survival
25	1958	Human	AV-ECLS	Rotating film	Yes	Yes	5-12 hours
26	1961	Lamb	VV-ECLS	Rotating disc	Yes	Yes	8-19 hours
27	1962	Dog	VV-ECLS	Rotating disc	Yes	Yes	2.5 hours
28	1962	Piglet	AV-ECLS	Rotating disc film	Yes	Yes	8 hours
56	1963	Lamb	AV-ECLS	Rotating disc film	Yes	Yes	40 minutes
29	1964	Lamb	AV-ECLS	Rotating disc film	Yes	No	1 hour
30	1964	Dog	AV-ECLS	Membrane	Yes	-	2-5 hours
12	1965	Lamb	AV-ECLS	Rotating disc film	No	Yes	0.3-3 hours
57	1968	Human	-	Coiled membrane	Yes	-	1.5-5 hours
58	1968	Lamb	AV-ECLS	Rotating disc film	Yes	Yes	24 hours
32	1969	Lamb	AV-ECLS	Silicone coiled	Yes	Yes	4-55 hours

TABLE 1 (continued)

Reference	Year	Model	Circuit	Oxygenator	Pump	Submersion	Survival
59	1979	Lamb	AV-ECLS	Microchannel membrane	Yes	No	-
38	1987	Goat	AV-ECLS	Silicone hollow fiber	Yes	Yes	Up to 165 hours
39	1989	Goat	AV-ECLS	Silicone hollow fiber	Yes	Yes	Up to 236 hours
40	1993	Goat	AV-ECLS	Silicone hollow fiber	Yes	Yes	Up to 542 hours
46	1998	Goat	AV-ECLS	Polyolefin hollow fiber	Yes	Yes	Up to 237 hours

TABLE 2 - Overview of recent experiments performed with several AP models

Reference	Year	Model	Circuit	Oxygenator	Pump	Submersion	Survival
60	2009	Lamb	AV-ECLS	Hollow fiber	No	No	4 hours
50	2011	Lamb	AV-ECLS	Polypropylene	No	No	3 hours
61	2012	Lamb	AV-ECLS	Membrane	No	Yes	Up to 30 hours
48	2012	Lamb	VV-ECLS	Polypropylene	Yes	Yes	24 hours
49	2013	Lamb	VV-ECLS	Polypropylene	Yes	No	70 hours
52	2014	Piglet	AV-ECLS	Microfluidic	No	No	4 hours
51	2014	Lamb	AV-ECLS	Polypropylene	No	No	6 hours
16	2015	Lamb	VV-ECLS	Polypropylene	Yes	No	Up to 1 week

ANEXOS

I - 2018 Update on "*Artificial Placenta: Recent Advances and Potential Clinical Applications*"

II - Editorial "*The Artificial Placenta: is Clinical Translation Next?*"

III - Citações do artigo "*Artificial Placenta: Recent Advances and Potential Clinical Applications*"

IV - Normas de publicação da revista científica Pediatric Pulmonology

V - Agradecimentos

2018 UPDATE ON "ARTIFICIAL PLACENTA: RECENT ADVANCES AND POTENTIAL CLINICAL APPLICATIONS"

In 2016, Miura and colleagues modified membranous oxygenators to test the hypothesis of a parallelized AP circuit[1], and compared it with the single-circuit AP. Parallelization of the AP system successfully decreased its resistance and prolonged low-weight lamb fetuses' survival up to 64 hours. Moreover, significantly low blood lactate levels were registered[1]. Further studies under a parallelized circuit were conducted, with lamb fetuses being kept in a physiologically stable condition for periods of 48 hours[2] and 1 week[3]. However, white-matter injury was reported in two out of five animals, in each experiment[1,2].

Aiming the study of cerebral perfusion and oxygenation, researchers from Michigan University ECLS Laboratory successfully maintained fourteen lambs under venovenous AP support for up to 92 hours[4]. Despite the fact that this particular circuit configuration presents high risk for cerebral hypoperfusion, spectroscopy and carotid arterial flow suggested that brain oxygen delivery was preserved[4] and that it poorly correlated with systemic oxygen saturation[4]. Further studies are necessary to assess white matter injury, and address the issue of intraventricular hemorrhage, even though necropsy evaluations showed no evidence of intracranial hemorrhage in their study[4].

This group of researchers recently concluded that intratracheal perfluorocarbon instillation during AP support prevents lung injury and maximizes lung development, in comparison with the previously preferred approach with amniotic fluid and tracheal occlusion[5]. Increased surfactant production was also reported[5]. With further development, the VV-ECLS may offer a feasible alternative for EPT infants.

In 2017, Flake and colleagues presented a unique AP system that incorporates a pumpless oxygenator through an umbilical vascular interface kept within a closed fluid circuit, the polyethylene Biobag[6]. This model, which resembles the womb environment in shape and size, allowed eight fetal lambs to grow in a temperature-controlled, near-sterile environment, breathing an amniotic-like fluid[6]. Swallowing an electrolyte solution improved fetal fluid homeostasis and provided an additional route for nutrition. Furthermore, since there was continuous fluid exchange, this configuration solved the problem of gross fluid contamination and infection[6].

In this study, double umbilical artery and single umbilical vein cannulation were preferred over carotid use, preserving a length of native umbilical cord between the cannula tips and the abdominal wall. This approach allowed vascular adaptation to pressure changes across the AV shunt[7] and was proven to optimize circuit flow dynamics and stability, since it closely relates to the placental physiology in comparison to other cannulation methods[7].

Remarkably, Flake et al. reported successful transition to air breathing after AP support in two lambs that were connected to the circuit for 21 and 29 days, respectively[8]. The animals presented satisfying responses to feeding and normal somatic growth[8]. One did not survive a pyelonephritis after 12 days of independent life, whereas the other reportedly surpassed three months survival with apparently normal neurological outcomes[8].

These results are historical and superior to all previous attempts of EPT lambs' ECLS in both duration and physiologic well-being. Researchers will carry on evaluating and refining this AP system, since it needs to be downsized for human infants, who are one-third the size of the experimental fetus lambs. The first clinical trial is expected to occur within five years.

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Editorial

The Artificial Placenta: Is Clinical Translation Next?

George B. Mychaliska, MD*

Despite significant advances in the treatment of prematurity including antenatal steroids, advanced mechanical ventilation strategies, and exogenous surfactant, the mortality and morbidity remain high for these vulnerable infants. In particular, the mortality and morbidity of extremely low gestational age newborns (ELGANs) defined as <28 weeks estimated gestational age (EGA), is extremely high.[1] A radical paradigm shift in the treatment of extreme prematurity would be to re-create the intra-uterine environment using an extracorporeal artificial placenta (AP).

In this issue, Metelo-Coimbra and Roncon-Albuquerque[2] review recent advances in the field and assess barriers to clinical translation. From the outset, it should be acknowledged that although there is a large number of premature births worldwide (defined as <37 weeks EGA), outcomes have substantially improved for infants >28 weeks EGA. Apart from some specific congenital anomalies like congenital diaphragmatic hernia, the AP is intended for the treatment of ELGANS who experience the most complications of prematurity and whose outcome remains poor.

The authors focus on lung immaturity and provide substantial evidence of the iatrogenic effects of mechanical ventilation on both lung injury and the deleterious cardiovascular effects.[2] It is worth noting that although ELGANS are predisposed to interventricular hemorrhage (IVH) given their immature germinal matrix, mechanical ventilation has been implicated in the pathogenesis of IVH by increasing intrathoracic and intracranial pressure with every breath.[3] The ELGANs who are never subjected to positive airway pressure have fewer complications of prematurity. An appreciation of the deleterious effects of mechanical ventilation and high oxygen concentrations on premature lungs has led to a dramatic shift toward less invasive ventilator strategies for premature infants. Although this strategy appears promising for some patients,[4] there is still a subset of ELGANS that cannot maintain adequate gas exchange with the most invasive ventilator strategies.

Although the pulmonary system is critical to initial survival and long-term pulmonary morbidity is high among survivors, there are other significant complications of ELGANs that warrant consideration. Predictable and unsolved complications associated with prematurity include neurologic injury (IVH, white matter injury), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and sepsis. Our current inability to prevent these complications relates both to organ immaturity and conventional treatment strategies such as positive pressure ventilation, that have historically been developed for full term infants. To potentially solve these problems, the AP must not only recreate the fetal milieu and provide life-sustaining functions such as adequate gas exchange and fetal hemodynamic stability, but it should also protect against organ trauma and allow the normal developmental pathways to occur.

An AP may appear far beyond the reach of modern science, but the idea of creating a life support system to maintain growing fetuses in a womb-like environment with extracorporeal support was first investigated 60 years

Section of Pediatric Surgery, Department of Surgery, Fetal Diagnosis and Treatment Center, University of Michigan Medical School, C.S. Mott Children's Hospital,, 1540 E. Medical Center Drive, SPC 4211, Ann Arbor, Michigan 48109.

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*Correspondence to: George B. Mychaliska, MD, Section of Pediatric Surgery, Department of Surgery, Fetal Diagnosis and Treatment Center, University of Michigan Medical School, C.S. Mott Children's Hospital, 1540 E. Medical Center Drive, SPC 4211, Ann Arbor, MI 48109.
E-mail: mychalis@med.umich.edu

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ago! Metelo-Coimbra and Roncon-Albuquerque provide a succinct review of AP terminology and history of milestones.[2] Since fetuses normally develop with extra-corporeal support, it should perhaps not surprise us that researchers were drawn to this concept shortly after the successful introduction of cardio-pulmonary bypass. For historians of science, it is noteworthy that researchers were on the right path, but got derailed many times due to the state of biomedical technology and insufficient knowledge of the physiology of premature infants. In my view, the history of the development of the AP is marked by many experimental failures with episodic successes. Despite incremental success, many research groups abandoned this work as progress was being made with antenatal steroids, exogenous surfactant, advanced mechanical ventilation strategies, and ECMO for term and near-term infants.

An appreciation of the unsolved problems of extreme prematurity coupled with recent advances detailed by the authors[2] has led to a resurgence of work on the AP. The fetal lamb is the best model, and the lamb gestational age which corresponds to ELGAN lungs is 118 days gestation (term = 145 days). Although the AP is promising and has the potential to radically change the treatment of prematurity, several obstacles remain. As the authors point out,[2] the first issue is the most effective ECLS configuration. A simple pumpless AV-ECLS circuit utilizing the umbilical vessels is appealing, but our experience demonstrated only short-term survival and declining cardiac function.[5] Despite cannulation of the umbilical arteries to the sheep aorta (to obviate vessel spasm) and adding a pump, matching extracorporeal flow to systemic flow is very difficult (the native placenta does this automatically). In addition, given the tortuosity, size, and spasm associated with human umbilical arteries, we transitioned to a pump-driven VV-ECLS model with inflow via the umbilical vein and outflow via the jugular vein. This approach provides 7 days of support with excellent gas exchange and hemodynamic stability.[6] With current technology, we believe this strategy is clinically translatable to extremely premature infants.

As mentioned previously, the AP strategy will require long-term support (2–4 weeks in humans) and demonstration that organs are maturing and protected from trauma. This corresponds to 10–14 days in the 118 day lamb model. As such, an in-depth study of lung development, long-term support, and weaning to a ventilator and air breathing will be required. A crucial aspect of lung development will be the airway strategy during AP support. In our early work, the fetal lambs were submerged in a warmed "amniotic bath" effectively re-creating the intrauterine environment.[5,7] While appealing in some regards, there are infection and patient access issues with this approach. More recently, we have been intubating the fetal lambs, filling them with amniotic fluid or Perflubron and either capping the endotracheal tube or maintaining 5–8 cm H_2O pressure. It is possible to harness the power of mechanotransduction with this approach and possibly accelerate lung growth.[8,9]

Apart from lung development which is crucial during AP support, other vulnerable premature organs need to be examined. Brain perfusion, function, and development are critical to understand. Although the sheep is not a good model for IVH, brain physiology and evidence of white matter injury can be assessed. With a high incidence of NEC in premature infants, optimal nutrition and perfusion of the gastrointestinal system warrants investigation. Long term survivors of the AP should be examined for evidence of retinopathy of prematurity. Lastly, renal and hepatic function should be addressed.

As a general rule, extracorporeal support is reserved for infants ≥ 34 weeks EGA due to a higher rate of IVH in extremely premature infants. The authors point out the feasibility of "preemie ECMO" in infants from 29 to 33 weeks,[2] but ELGANs would have prohibitively high rates of IVH. As such, a critical barrier to clinical application will be the development of non-thrombogenic surfaces that will obviate the need for anti-coagulation.[10,11] Lastly, clinical application will require a clinical prognostication tool to select premature infants at the highest risk for mortality on the first day of life.[12]

Given recent advances and ongoing work, we believe that the AP will be used in ELGANs in the next 5 years.

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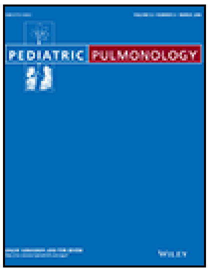

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